

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant : Daniel Pinto et al. Art Unit : Unknown
Serial No. : New Filing Examiner : Unknown
Filed : Herewith
Title : REGULATORY SEQUENCE OF THE MOUSE VILLIN GENE - USE IN
TRANSGENESIS

Box Patent Application
Commissioner for Patents
Washington, D.C. 20231

PRELIMINARY AMENDMENT

Sir:

Prior to examination, please amend the application as follows:

In the specification:

Please insert the following paragraph:

Page 1, line 1

--This is a continuation of International Application PCT/EP98/08009, with an international filing date of December 9, 1998.--

In the claims:

Amend claims 4-8, 10-16, 19-21, 23, 24, 26, 27 and 30 as follows:

4. (Amended) Nucleotide sequence according to claim 1, which comprises the nucleotide fragment extending from the HS I to the HS IV Dnase I-hypersensitive sites.

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June 8, 2001
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5. (Amended) Nucleotide sequence according to claim 1, comprising a nucleotide fragment extending from the HS IV Dnase-hypersensitive site to the translation initiation site of the murine villin gene.

6. (Amended) Nucleotide sequence according to claim 1, which comprises a nucleotide fragment extending from the nucleotide at around position -100 upstream from the transcription initiation site, to the translation initiation site.

7. (Amended) Nucleotide sequence according to claim 1, which comprises a nucleotide fragment extending 3.5 kb upstream from the transcription initiation site to the transcription initiation site and further comprises the translation initiation site.

8. (Amended) Nucleotide sequence according to claim 1, which comprises a nucleotide fragment extending from around the nucleotide at position -480 from the transcription initiation sequence, to the translation initiation site.

10. (Amended) Nucleotide sequence according to claim 1-which is mutated by deletion of one or several nucleotides, within the nucleotide fragment of 5.5 kb corresponding to intron 1 extending from position 47 starting from the transcription initiation site, provided that said mutation does not affect the presence of the HS II Dnase I-hypersensitive site.

11. (Amended) Nucleotide sequence according to claims 1, which comprises nucleotide regions having a regulatory activity affecting the level of expression of the murine villin gene.

12. (Amended) Nucleotide sequence according to claim 1, which is derived from the nucleotide sequence of the murine villin gene having a size of 9 kb on an agarose gel and extending 3.5 kb upstream from the transcription initiation site and 5.5 kb downstream from said site, or a fragment thereof, said nucleotide sequence or fragment thereof having a regulatory

activity on the level of expression of the murine villin gene in intestine cells and/or in transgenic mice.

13. (Amended) Recombinant nucleotide sequence comprising a first nucleotide sequence according to claim 1 and a second nucleotide sequence for which a tissue specific targeted expression in epithelial intestine cells is sought.

14. (Amended) Recombinant nucleotide sequence according to claim 13, wherein the second nucleotide sequence is a sequence encoding a determined polypeptide.

15. (Amended) Recombinant nucleotide sequence according to claim 13, wherein the second nucleotide sequence is a sequence of therapeutic interest.

16. (Amended) Recombinant nucleotide sequence according to claim 13, wherein the second nucleotide sequence is an oncogene.

19. (Amended) Recombinant nucleotide sequence according to claim 13 which further comprises a third nucleotide sequence consisting of a reporter sequence under the control of said first nucleotide sequence.

20. (Amended) Recombinant nucleotide sequence according to claim 13 wherein the second nucleotide sequence is placed under the control of an inducible system.

21. (Amended) Recombinant cell comprising a recombinant sequence according to claim 13.

23. (Amended) Recombinant cell according to claim 21, which is a stem cell.

24. (Amended) Recombinant cell according to claim 21, which is a differentiated cell.

26. (Amended) Recombinant cell according to claim 21 which is immortalized.

27. (Amended) Transgenic animal expressing a recombinant nucleotide sequence according to claims 14.

30. (Amended) Process for the preparation of a transgenic mouse, comprising the steps of:

administering the recombinant nucleotide sequence of claim 14 into the pronuclei of fertilized eggs of mice;
enabling the development of the recombined eggs to recover transgenic mice (founders); and
verifying the presence of the transgene.

Please add new claim 31 as follows:

31. (New) Process of claim 30, further comprising crossing the founders with non transgenic mice.

In the abstract:

Please insert the following abstract:

--The invention relates to regulatory sequences of the mouse villin gene that efficiently drive transgenic expression in immature and differentiated epithelial cells of the intestine and uro-genital tracts. The invention also relates to recombinant constructs comprising said regulatory sequences, for the control of the targeted expression of determined nucleic acid sequences so-called (heterologous sequences or also transgenes), in cells or tissues originating from the intestinal mucosa. A further object of the invention is to provide cells, tissues or organisms including animals, expressing said determined nucleic acid sequences in a targeted manner.--

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Attorney's Docket No.: TC-04543-RCL-060801-1

REMARKS

Attached is a marked-up version of the changes being made by the current amendment.

Applicant requests consideration and allowance of claims 1-31. Please apply any other charges or credits to Deposit Account No. 06-1050.

Respectfully submitted,

Date: June 8, 2001

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VERSION WITH MARKINGS TO SHOW CHANGES MADE

In the specification:

Please insert the following paragraph:

Page 1, line 1

--This is a continuation of International Application PCT/EP98/08009, with an international filing date of December 9, 1998.--

In the claims:

Claims 4-8, 10-16, 19-21, 23, 24, 26, 27 and 30 have been amended as follows:

4. (Amended) Nucleotide sequence according to ~~anyone of~~ claims 1 ~~to~~ 3, which comprises the nucleotide fragment extending from the HS I to the HS IV Dnase I-hypersensitive sites.

5. (Amended) Nucleotide sequence according to ~~anyone of~~ claims 1 ~~to~~ 4, comprising a ~~the~~ nucleotide fragment extending from the HS IV Dnase-hypersensitive site to the translation initiation site of the murine villin gene.

6. (Amended) Nucleotide sequence according to claim 1, which comprises a ~~the~~ nucleotide fragment extending from the nucleotide at around position -100 upstream from the transcription initiation site, to the translation initiation site.

7. (Amended) Nucleotide sequence according to claim 1, which comprises a ~~the~~ nucleotide fragment extending 3.5 kb upstream from the transcription initiation site to the transcription initiation site and further comprises the translation initiation site.

8. (Amended) Nucleotide sequence according to claim 1, which comprises a ~~the~~ nucleotide fragment extending from around the nucleotide at position -480 from the transcription initiation sequence, to the translation initiation site.

10. (Amended) Nucleotide sequence according to ~~anyone of~~ claims 1 ~~to~~ 9 which is mutated by deletion of one or several nucleotides, within the nucleotide fragment of 5.5 kb corresponding to intron 1 extending from position 47 starting from the transcription initiation site, provided that said mutation does not affect the presence of the HS II Dnase I-hypersensitive site.

11. (Amended) Nucleotide sequence according to ~~anyone of~~ claims 1 ~~to~~ 8, which comprises nucleotide regions having a regulatory activity affecting the level of expression of the murine villin gene.

12. (Amended) Nucleotide sequence according to claim 1, which is derived from the nucleotide sequence of the murine villin gene having a size of 9 kb on an agarose gel and extending 3.5 kb upstream from the transcription initiation site and 5.5 kb downstream from said site, or a fragment thereof, said nucleotide sequence or fragment thereof having ~~have~~ a regulatory activity on the level of expression of the murine villin gene in intestine cells and/or in transgenic mice.

13. (Amended) Recombinant nucleotide sequence comprising a first nucleotide sequence according to ~~anyone of~~ claims 1 ~~to~~ 12 and a second nucleotide sequence for which a tissue specific targeted expression in epithelial intestine cells is sought.

14. (Amended) Recombinant nucleotide sequence according to ~~anyone of~~ claim 13, wherein the second nucleotide sequence is a sequence encoding a determined polypeptide.

15. (Amended) Recombinant nucleotide sequence according to ~~anyone of~~ claims 13 ~~to~~ 14, wherein the second nucleotide sequence is a sequence of therapeutic interest.

16. (Amended) Recombinant nucleotide sequence according to ~~anyone of~~ claims 13 ~~to~~ 15, wherein the second nucleotide sequence is an oncogene.

19. (Amended) Recombinant nucleotide sequence according to ~~anyone of~~ claims 13 to ~~18~~ which further comprises a third nucleotide sequence consisting of a reporter sequence under the control of said first nucleotide sequence.

20. (Amended) Recombinant nucleotide sequence according to ~~anyone of~~ claims 13 ~~1 to 19~~ wherein the second nucleotide sequence is placed under the control of an inducible system.

21. (Amended) Recombinant cell comprising a recombinant sequence according to ~~anyone of~~ claims 13 to ~~20~~.

23. (Amended) Recombinant cell according to claim 21 ~~22~~, which is a stem cell.

24. (Amended) Recombinant cell according to claim 21 ~~22~~, which is a differentiated cell.

26. (Amended) Recombinant ~~epithelial~~ cell according to ~~anyone of~~ claims 21 ~~22 to 25~~ which is immortalized.

27. (Amended) Transgenic animal expressing a recombinant nucleotide sequence according to ~~anyone of~~ claims 14 to ~~21~~.

30. (Amended) Process for the preparation of a transgenic mouse animal, ~~especially a transgenic mice~~ comprising the steps of:

administering the recombinant nucleotide sequence of claim 14 ~~administration of a transgene~~ into the pronuclei of fertilized eggs of mice;
- enabling the development of the recombined eggs to recover transgenic mice (founders); and
verifying the presence of the transgene;

~~--if appropriate, crossing the founders with non transgenic mice.~~

Please add new claim 31 as follows:

31. (New) Process of claim 30, further comprising crossing the founders with non transgenic mice.

In the abstract:

Please insert the following abstract:

--The invention relates to regulatory sequences of the mouse villin gene that efficiently drive transgenic expression in immature and differentiated epithelial cells of the intestine and uro-genital tracts. The invention also relates to recombinant constructs comprising said regulatory sequences, for the control of the targeted expression of determined nucleic acid sequences so-called (heterologous sequences or also transgenes), in cells or tissues originating from the intestinal mucosa. A further object of the invention is to provide cells, tissues or organisms including animals, expressing said determined nucleic acid sequences in a targeted manner.--